

REMARKS/ARGUMENTS

Reconsideration of the present application, as amended, is respectfully requested.

A. STATUS OF THE CLAIMS

As a result of the present amendment, claims 1, 5, 9, 11, 15-26 are presented in the case for continued prosecution. New claims 17-26 have been added. Support for the new claims can be found in the specification and within the claims as originally filed in the application. See, for example, page 7, line 5 for claim 17; page 22, lines 9, *et seq.* for claims 18-21; page 40, Example 17 for claim 22; and page 4, lines 20-25 for claims 23-26. No new matter has been added.

B. THE INVENTION

The presently claimed invention relates to polymer conjugates containing biologically active compounds. As pointed out on page 8 of the specification, beginning at line 12:

"There are several advantages associated with these types of polymers. For example, depending upon the linkages used to attach the polymer strands to the multifunctional spacer groups, the artisan can design relatively high molecular weight polymeric transport systems which will predictably biodegrade into polymers of relatively low molecular weight which are more readily eliminated from the body than the singular polymer of higher molecular weight. Secondly, because relatively small molecular weight polymers are used to build the biodegradable transport form, the polydispersity associated with some single strand high molecular polymers such as when PEG has a molecular weight of over 40 kDa is substantially avoided." (emphasis added).

Page 9, lines 16-19 provide a description of further advantages associated with the species of Formula (X) which is currently being examined. Specifically, the passage states:

"In the case of compounds corresponding to formula (X), the artisan is provided with a unique polymer transport form which can deliver more than one equivalent of biologically active material using a backbone which includes multiple strands of polymer."

Such advantages are different from the attributes of polymer conjugates having a single high molecular weight polymer strand attached to a biologically active material.

C. OBJECTIONS TO SPECIFICATION AND REJECTIONS UNDER 35 U.S.C. §112

On page 2 of the Office Action, the Examiner has objected to the specification. Applicants have amended the specification to insert the U.S. patent number corresponding to U.S. patent application number 09/293,557. Furthermore, the underlined terminology in the specification has now been italicized.

On page 3 of the Office Action, the Examiner has rejected the subject matter of claims 5 and 9 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. In response, Applicants have amended the claims and it is urged that they are in proper form in all respects.

D. REJECTION UNDER 35 U.S.C. § 103(a)

1. Greenwald et al. (6,011,042) in view of Greenwald, et al., J. Med. Chem. (1996) and Greenwald, et al. (5,965,566)

On pages 3-5 of the Office Action, the Examiner has rejected the subject matter of claims 1, 5, 9, 11, 15 and 16 as being obvious over commonly assigned U.S. Patent No. 6,011,042 (Greenwald, et al.) in view of Greenwald, et al., J. Med. Chem. (1996) and commonly assigned U.S. Patent No. 5,965,566 (Greenwald, et al.). The Examiner has taken the position that it would have been obvious to one of ordinary skill to make a biodegradable polymeric conjugate at the 20-O position of camptothecin to treat mammals in view of this combination of references.

Applicants respectfully traverse the rejection of the Examiner and it is urged that a proper *prima facie* case of obviousness has not been made by the Examiner. A *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. The art must suggest how to apply its teachings to the specifically claimed invention. The legal standard for

maintaining a *prima facie* allegation of obviousness has been stated in many different ways, which can be summarized as follows. A *prima facie* allegation of obviousness can be maintained,

"only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

Here, Applicants respectfully assert that the references cited by the Examiner fail to suggest how to combine their respective teachings to arrive at the claimed biodegradable polymeric prodrug conjugates.

The present invention is directed to biodegradable, polymeric-based conjugates having increased therapeutic payloads. More specifically, as a result of the restriction requirement instituted by the Examiner, Applicants direct the Examiner to the compound identified as 17 in the specification, (see Example 17, figure 12b and claim 22). The inventive compounds thus include two equivalents of polymer (PEG) separately attached to a linking system which also attaches two equivalents of a biologically active composition, camptothecin. A key point of distinction for the Examiner to take note of is the fact that unlike the references relied upon, the conjugates of the claimed invention do not employ a polymer to act as the spacer between the equivalents of the drug. Instead, the polymer strands of the inventive compounds are attached to one portion of the multifunctional linker and the active compounds are in much closer proximity to each other by virtue of their attachment to the same multifunctional linkage system. The prior art uses separate linkages for each biologically active compound attached. The references relied upon by the Examiner thus teach unrelated polymeric conjugates.

The '042 patent cited by the Examiner discloses aromatic amino acid esters of camptothecin using the 10-hydroxy position for polymeric attachment. The Examiner has also admitted that the '042 patent does not teach 20-O-esters. It can be seen that the polymer-linker system is significantly different from that employed by Applicants herein. The '042 patent employs a single polymer strand which can have one equivalent of drug attached at each terminal of the polymer. For ease of discussion, the '042 patent describes systems based on the premise of:

Drug-Linker-PEG-Linker-Drug.

There is no disclosure concerning how to use a single linker system to allow direct attachment of more than one equivalent of drug thereto, let alone one that achieves this result and also facilitates attachment of more than one polymer strand as the present invention does. Applicants therefore urge that contrary to the position of the Examiner, the claimed invention is not rendered obvious by the commonly assigned '042 patent.

The J. Med.Chem. does not cure the deficiencies of the '041 patent. It merely describes another polymeric system in which two equivalents of drug (camptothecin) are attached through separate linkers to the opposite ends of a single polymer strand. See compound 3b of the reference. The '566 patent also relied upon by the Examiner essentially provides the same teaching as the J. Med.Chem. paper. It thus discloses a polymer-linker-transport system that is unlike the multifunctional linker based polymer systems claimed herein.

In view of the vast differences between the claimed compositions and the prior art, it is urged that the methods of preparing the same described in claim 15 and method of treatment described in claim 16 are also distinguishable thereover. It is respectfully submitted that the claimed invention is not rendered obvious by the combination of references related upon by the Examiner.

2. Conclusion concerning rejection under 35 U.S.C. § 103

In view of the above arguments, it is respectfully submitted that Applicants have obviated the rejection under 35 U.S.C. § 103. It is also submitted that no *prima facie* case of obviousness has been established. Applicants have shown that the combination of references is not the invention and does not suggest the invention. Reconsideration and removal of the rejection is therefore proper and requested.

E. EXTENSION OF TIME PETITION

This response is being filed with a petition for a one month extension of time. A credit card payment authorization form is enclosed for payment of the fee due for the one month extension of time. No further fees are believed to be required. If any further fees are due, please charge the fee to Deposit Account Number 02-2275.

F. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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April 30, 2004

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